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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/423,905 | 04/24/2000 | TOHRU TANI | FJN-077 | 7282 |

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|---|
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

DATE MAILED: 12/16/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) |
|---|---|---|
| | 09/423,905 | Tani et al |
| | Examiner | Group Art Unit |
| | Duffy | 1645 |

*—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

☒ Responsive to communication(s) filed on 9-23-02 (Response, formal drawing, certified translation)

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

**Disposition of Claims**

☒ Claim(s) 2-23 is/are pending in the application.

Of the above claim(s) 12, 23 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 2-11 + 13-22 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claim(s) 2-23 are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119 (a)-(d)**

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

**Attachment(s)**

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 9-23-02 ☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892 ☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948 ☐ Other _____

**Office Action Summary**

## DETAILED ACTION

### *Response to Amendment*

1. The amendment and certified translation filed 9-23-02 have been entered into the record. Claims 2-11 and 13-22 are under examination.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

### *Drawings*

3. The Formal drawings were received on 9-23-02. These drawings are acceptable.

### *Information Disclosure Statement*

4. References CAH and CAJ have been considered. An initialed copy of the references have been provided. References CAC and CAD will not be considered. These references are not in English and as indicated on the copy of the 1449, no English abstract has been provided. MPEP 609 citing 37 CFR 1.98 provides that I) A concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56© most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language. The concise explanation may be either separate from applicant 's specification or incorporated therein.

(ii) A copy of the translation if a written English-language translation of a non-English-language document, or portion thereof, is within the possession, custody, or control of, or is readily available to any individual designated in § 1.56© is required for non-English documents. Neither of (I) or (ii) have been provided for CAC and CAD and as such these references have not been considered.

## *Election/Restriction*

5. This application contains claims 12 and 23 drawn to an invention nonelected with traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

## *Rejections Withdrawn*

6. The rejection of claims 2-11 under 35 U.S.C. 102(a) as being anticipated by WO 98/41230 (Reference BO on PTOL-1449) or WO98/40096 (Reference BP on PTOL-1449) is withdrawn based on Applicants filing of a certified translation of the Japanese priority document.

7. The rejection of claims 2-11 and 13-22, under 112, second paragraph for the recitation of the acronym TCF-II is indefinite, while acronyms are permitted in the claims, the first appearance of the acronym should be preceded by it full name is obviated by Applicants' amendment.

8. The rejection of claims 2-11, under 112, second paragraph for the term "treatment" is indefinite as it relates to sepsis because it is unclear what aspects of sepsis are being

treated. For example, sepsis includes fever, chills, tachycardia, somnolence, bacteremia, thrombocytopenia, circulatory breakdown, and failure of multiple organs, is obviated by Applicants' amendments.

## *Rejections Maintained*

9. The rejection of claims 4 and 15 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons made of record in Paper No. 14, mailed 4-22-02.

Applicants' arguments have been carefully considered but are not persuasive. Applicants argue that the specification provides for recombinant expression of TCF-II. However, the claims are directed to a cell based therapeutic "expressing a recombinant DNA encoding TCF-II in a host cell, thereby to prepare the therapeutic agent", the "therapeutic agent" being a cell expressing TCF-II. This issue may be resolved by applicants amending the claim to state that "the TCF-II is produced recombinantly". While the relied upon passages provide for recombinant expression of TCF-II they do not provide written description for cell-based therapeutics (i.e. administering a cell producing TCF-II).

10. Claims 2-11 and 13-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the survival rate of sepsis in a mammal by decreasing lipopolysaccharide (LPS)-induced bacterial translocation in the intestine comprising administering to the mammal an amount of isolated or purified tissue cytotoxic factor - II (TCF-II) sufficient to decrease LPS-induced bacterial

translocation in the intestine thereby increasing the survival rate of sepsis, it does not reasonably provide enablement for unpurified TCF-II, all aspects of treatment of sepsis, all types of sepsis, cell therapy, prevention of sepsis or use of polysaccharide chains or variants thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims is maintained for reasons made of record in Paper No. 14, mailed 4-22-02.

Applicants arguments have been carefully considered but are not persuasive. Applicants argue that the specification enables the reduction of sepsis associated lethality regardless of the route of infection. Applicants argue that the showing that TCF-II is effective in reducing lethality because it prevents systemic invasion by intestinal flora when the cecum is punctured. This is not persuasive, Applicants own examples indicate that systemic invasion is not "prevented" and that numbers of bacteria do in fact penetrate the intestinal barrier. Further, the examples were drawn only to lipopolysaccharide ( LPS)-mediated translocating bacteria and not any other types of sepsis cause by other bacteria such as *Staphylococcus aureus*, that do not have LPS. Applicants have not demonstrated that TCF-II is effective in reducing lethality when the microorganism is established in the bloodstream or is mediated by other triggering events or other types of bacteria that do not have LPS or enter by other means. Applicants have clearly established that TCF-II operates by reducing LPS-induced translocation of bacteria and reduces the amount of systemic bacteria, thereby reducing lethality. The specific event where TCF-II operates is in the translocation and there is no evidence of record that any post LPS-induced bacterial translocation event is effected (i.e. growth rate of bacteria, lethality). Therefore, there is no indication that LPS-bacteria or any

other bacteria introduced into the bloodstream by other routes would be similarly affected because the LPS-translocating machinery is not present in these other sites (catheters, skin etc.). Therefore a mechanism that is operative in the intestine does not readily translate to mechanisms of invasion in the skin or by a catheter or prosthesis and does not apply to other bacteria that do not have LPS. Since Applicants have not demonstrated that TCF-II is effective in reducing translocation or effective post-translocation reducing lethality in any animal model it is not enabled for such. Neither of the examples indicate effective treatment post translocation and the examples are limited to indicate that the treatment was given prior to injury and not after injury has taken place it is only enabled for "a method of increasing the survival rate of sepsis in a mammal by decreasing lipopolysaccharide (LPS)-induced bacterial translocation in the intestine comprising administering to the mammal an amount of isolated or purified tissue cytotoxic factor - II (TCF-II) sufficient to decrease LPS-induced bacterial translocation in the intestine thereby increasing the survival rate of sepsis". It is not routine in the art to discover if administering TCF-II post injury is effective in reducing lethality or is effective for other routes of invasion and other different bacteria, that is in fact the essence of invention. The mechanisms of translocation of LPS-mediated bacterial translocation in the intestine are not present in the alleged other triggering events and as such, reducing LPS-mediated bacterial translocation and is subsequent reduction in sepsis associated lethality does not and can not apply to other triggering events that are not mediated by this mechanism. Burns and the associated breakdown of epithelia, do not provide for LPS-mediated translocation and as such, reducing intestinal LPS-mediated bacterial translocation in these patients would not lead to reduction in lethality of sepsis. As such, Applicants arguments of "routine experimentation" is not persuasive when similar

mechanisms are not in effect and clearly one skilled in the art would not have a reasonable expectation of success, when clearly the mechanisms of invasion and penetration are different. Applicants also argue that the specification similarly enables the reduction of bacterial translocation and indicates that TCF-II significantly suppresses LPS-induced translocation from the intestine. Applicants arguments are not commensurate in scope with the claims. The claim include all bacteria and all mechanisms of translocation. The specification is devoid of any translocation mechanism other that intestinal LPS-mediated bacterial translocation and fails to provide any similar translocating machinery for bacteria that lack LPS. Further the specification fails to teach other bacterial translocating mechanisms and demonstrate, in a representative number of models TCF-II reduces or suppresses bacterial translocation in general. Therefore the claims remain not-enabled for their full scope.

Applicants further argue that claims 4 and 15 are not drawn to the administration of cells producing TCF-II. The examiner strongly disagrees. The claims recite "expressing a recombinant DNA encoding TCF-II in a host cell, thereby to prepare the therapeutic agent". This claim language clearly indicates that the recombinant host cell is the therapeutic agent. Applicants are directed to the new matter rejection above for language in order to obviate this rejection.

As to claims 11 and 22, it is noted that the TCF-II comprises a polysaccharide chain, the claims do not indicate that TCF-II *further comprise a polysaccharide chain as is argued*. Applicants indicate that the prior art on page 4 is fully enabling for "polysaccharide chains" . The relied upon prior art indicates that TCF-II may be produced in a glycosylated or non-glycosylated form (synthetic). The prior art does not indicate how to vary the polysaccharide chain or vary the points of glycosylation. The claims currently

encompass a wide variety of polysaccharide chains and glycosylations not described in the prior art. The specification and the prior art fails to teach the exact chemical structure of any polysaccharide chains attached to native or recombinant TCF-II . as result, the specification fails to provide any written description of how to modify any polysaccharide chain attached to TCF-II, native or otherwise, *to achieve a functional therapeutic*. There is no guidance in this specification of how to modify the polysaccharide side chain. There is no starting point for variation and no description of how to achieve a polysaccharide chain variant. The specification has no apparent description of how to make and use polysaccharide. Applicants are invited to point to the page and line number in the specification where written description can be found for how to make and use these polysaccharide. While the courts have that a patent need not teach, and preferably omits, what is well known in the art. The omission of all details of how to make and use the product comprising different polysaccharide chains can not constitute an enabling specification. In the instant case there is no disclosure of any conditions under which the polysaccharide chains or variants thereof can be made and used. The specification is apparently devoid of any description of how to make and use such polysaccharide. As such, the failure of this specification of how to make and use the polysaccharide or variants thereof constitutes undue experimentation and is maintained for reasons made of record.

11. Claims 2 and 22 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons made of record in Paper Nol 14, mailed 4-22-02.

As to claims 11 and 22, TCF-II is described in the specification as a polypeptide. Applicants arguments have been carefully considered but are not persuasive. Applicants

indicate that this is not a redefinition of TCF-II as a polysaccharide chain and that the TCF-II must include a polysaccharide. This argument is not commensurate in scope with the claim. Applicants are arguing that *TCF-II further comprises a polysaccharide chain* and the claim does not set forth this concept.

## *Status of Claims*

12. All claims stand rejected.

## *Conclusion*

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Thursday and Saturday from 10:30 AM to 7:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
December 15, 2002

Patricia A. Duffy

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600